Pergamon

Tetrahedron Letters 43 (2002) 607–609

TETRAHEDRON LETTERS

Oxazoline azomethine imines preparation and cycloaddition with phenyl isocyanate

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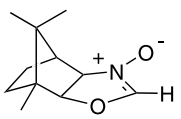
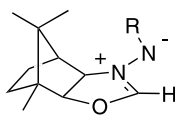
Received 9 November 2001; revised 22 November 2001; accepted 23 November 2001

Abstract—Various camphor derived oxazoline azomethine imines were prepared. These unstable dipoles led to cycloadducts in the presence of phenyl isocyanate.

Oxazoline-*N*-oxides **1** are useful dipoles which react with various dipolarophiles.[1] These cycloadditions led to the stereoselective syntheses of a number of natural products and analogues.[2] We present in this paper the preparation of their nitrogen counter part, oxazoline azomethine imine **2**, and a study of the reactivity of these dipoles in [2+3] cycloadditions.



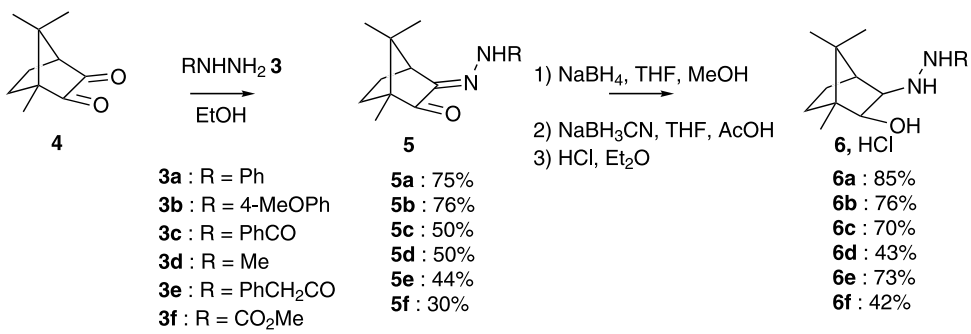
(+)-**1**



(+)-**2**

Several azomethine imines have been used as dipoles for the preparation of pyrazolidines[3] and an asymmetric version of these cycloadditions has been described recently.[4] Oxazolines derived azomethine imines such as compound **2**, which to the best of our knowledge are not described in the literature, could be of interest from several points of view. The possibility of introducing an electron-withdrawing or electron-donating functional group on the exocyclic nitrogen could allow a modulation of both reactivity and regioselectivity with several kinds of dipolarophiles. Furthermore, by analogy with oxazoline-*N*-oxide **1**, cycloadditions of dipoles **2** with α,β-unsaturated esters could lead after hydrolysis to non-racemic β-substituted amino acids.

Hydrazino*iso*borneol derivatives **6a**–**6f**, which are direct precursors of dipoles **2a**–**2f**, were prepared in a three-step sequence by analogy with the oxazoline–*N*-oxides series according to the general Scheme 1. Condensation of hydrazine derivatives **3a**–**3f** with camphorquinone **4** afforded the corresponding hydrazobornanone derivatives **5a**–**5f** which were isolated and purified by crystallisation in ethanol. Hydrazones **5a**–**5f** were in turn sequentially reduced with sodium borohydride and then with sodium cyanoborohydride in acidic medium. In all



Scheme 1.

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PII: S0040-4039(01)02244-4

cases the unstable hydrazo*iso*borneol intermediates were not purified, but directly engaged in the following reduction. As observed previously for the preparation of precursors dipoles **1**, these reductions were highly stereoselective. Compounds **6a**–**6f** were finally isolated by crystallisation as hydrochloride salts after treatment with HCl gas in anhydrous ether.

As in the case of oxazoline-*N*-oxide **1**, dipoles **2** were unstable and attempted isolation was precluded by a rapid hydrolysis. For this reason, dipoles **2** were directly submitted to cycloaddition with a very reactive dipolarophile, phenyl isocyanate, and the optimisation of the dipole formation was followed by this two-step sequence using hydrazine hydrochloride **6a** as a model dipole precursor.

As summarised in Table 1, the formation of dipole **2a** was performed in toluene or dichloromethane in the presence of molecular sieves 4 Å and of an excess of trimethyl orthoformate. In some cases, calcium carbonate was also introduced at this stage, instead of triethylamine introduced after dipole formation (entries 1 and 3). Phenyl isocyanate (5 equiv.) was then introduced alone (entries 1 and 3) or with triethylamine (entries 2 and 4–7). Cycloadditions were achieved in all cases at 40°C for 1 h. The excess of phenyl isocyanate was quenched with methanol and the cycloadduct **7a** was purified by chromatography. When hydrazino derivative **6a** was used as a base, the yield was quite low (entry 6). This experiment showed that the presence of 1 equiv. of hydrochloric acid is necessary for dipole formation. Thus, introduction of triethylamine after dipole formation gave better results than the introduction of calcium carbonate at the beginning of the reaction sequence (entries 3 and 4). Comparison between entries 4 and 5 showed that a large excess of trimethyl orthoformate (entry 5: 20 equiv.) increased the overall yield. Molecular sieves are used to trap methanol. However, in all cases, yields for this two-step sequence remained modest with hydrazino derivative **6a**.

The following reaction conditions were selected for the preparation and the cycloaddition of other dipoles **2b**–**2f**: $HC(OMe)_3$ (5 equiv.), molecular sieves 4 Å, toluene, 70°C, 4 h; then Et_3N (2 equiv.), PhNCO (5 equiv.), 70°C, 2 h.

As indicated in Scheme 2, yields of cycloadducts were highly dependent on the nature of the substituent on nitrogen. Best results were obtained with phenylacetyl and methoxycarbonyl groups (hydrazino derivatives **6e** and **6f**). With the more electron withdrawing benzoyl group, compound **6c**, no cycloadduct was obtained; in this case, formation of dipole **2d** is probably precluded by the poorer nucleophilicity of the basic nitrogen. With the methyl substituted compound **6d**, dipole was unstable and led to degradation products. Comparison between **6a** and **6b** showed that, contrary to our expectation, the presence of an electron-donating group has little influence on the overall yield.[5]

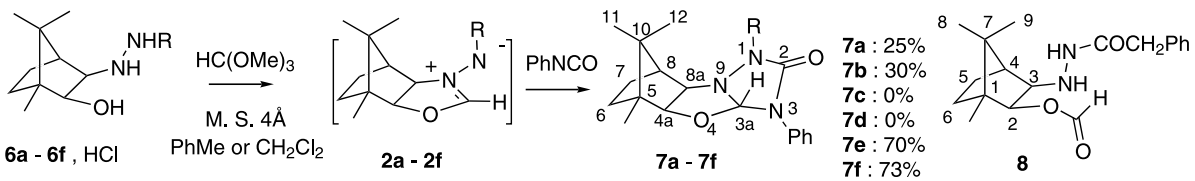
Cycloadditions were highly stereoselective and NOE experiments in the case of adduct **7f** showed a spatial proximity between C_{3a}-H and C_{12}-H_3. Similarly to cycloadditions with dipole **1**, the presence of C_{12} methyl prevents the approach of phenyl isocyanate by the β-face of the dipole.

The extension of use of the most promising dipole **2e** and various dipolarophiles was afterwards studied. Unfortunately, dipolarophiles such as cyclopentadiene, styrene, methyl crotonate and dimethyl maleate were unreactive under the above reaction conditions. In these experiments, compound **8** which is the result of

Table 1. Preparation of adduct **7a**: formation dipole **2a** and cycloaddition with phenyl isocyanate

Entry	Solvent	Base	Time (h)[c]	Temp. (°C)[c]	$HC(OMe)_3$ (equiv.)	Yield (%) **7a**
1	CH_2Cl_2	$CaCO_3$[a]	4	40	2	15
2	CH_2Cl_2	Et_3N[b]	4	40	2	19
3	PhMe	$CaCO_3$[a]	4	70	2	15
4	PhMe	Et_3N[b]	4	70	2	26
5	PhMe	Et_3N[b]	4	70	20	34
6	PhMe	None	4	70	2	8
7	PhMe	Et_3N[b]	8	70	2	24

[a] Introduce before dipole formation.
[b] Introduce after dipole formation.
[c] Time and temperature for dipole formation.



Scheme 2.

hydrolysis of dipole **2e** was the only product isolated. The use of nitroalkenes which were highly reactive dipolarophiles with dipole **1**[6] was in turn examined. Attempted cycloaddition between dipole **2f**, prepared from **6f**, and 1-nitrocyclohexene and nitrostyrene gave rise to degradation products. This poor reactivity contrasts sharply with the results observed with oxazoline-*N*-oxide **1**.

In conclusion, we describe in the present paper the first evidence for the formation of the unstable oxazoline azomethine imine dipoles and their stereoselective cycloadditions with phenyl isocyanate. The poor reactivity of these compounds precluded their use in cycloadditions with other dipolarophiles. However, preparation of differently substituted hydrazino derivatives and the possible use of other reactive dipolarophiles such as ketene derivatives open the way to further studies in this field.

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5. Selected data: ^{1}H NMR (200 MHz, δ ppm, TMS = 0, J: Hz, $CDCl_3$): compound **5e**: 7.4–7.24 (5H, m, ArH); 4.10 (2H, s, CH_2); 3.01 (1H, d, $J=4$, C_4-H); 2.08–1.74 (2H, m, C_5-H_a and C_6-H_a); 1.65–1.3 (2H, m, C_5-H_b and C_6-H_b); 1.05 (3H, s, C_8-H_3); 0.97 (3H, s, C_9-H_3); 0.84 (3H, s, C_{10}-H_3). Compound **6e** (250 MHz, $CDCl_3$): 7.34–7.20 (5H, m, ArH); 3.57 (1H, d, $J=7.4$, C_2-H); 3.50 (2H, s, CH_2); 2.77 (1H, d, $J=7.4$, C_3-H); 1.76 (1H, d, $J=4.3$, C_4-H); 1.70–1.58 (1H, m, C_5-H_a); 1.49–1.35 (1H, m, C_6-H_a); 1.0 (3H, s, C_9-H_3); 0.96–0.83 (2H, m, C_5-H_b and C_6-H_b); 0.91 (3H, s, C_8-H_3); 0.75 (3H, s, C_{10}-H_3). ^{13}C NMR (62.5 MHz, CD_3OD): 171, (C=O); 134.9, 130.2, 129.6, 128.3, (CAr); 78.1 (C_2); 71.2 (C_3); 50.4 (C_1); 48.9 (C_4); 46.7 (C_7); 40.9 (CH_2); 32.7, (C_6); 27.2 (C_5); 21.7, 21.1 (C_8 and C_9); 11.2 (C_{10}). Compound **7e** (200 MHz, $CDCl_3$): 7.65–7.25 (10H, m, ArH); 6.29 (1H, s, C_{3a}-H); 4.34 (2H, s, CH_2); 4.11 (1H, d, $J=7.3$, C_{4a}-H); 3.11 (1H, d, $J=7.3$, C_{8a}-H); 2.54 (1H, d, $J=4.3$, C_8-H); 1.80–1.22 (2H, C_7-H_a and C_6-H_a); 1.08 (3H, s, C_{11}-H_3); 1.01 (3H, s, C_{12}-H_3); 0.98–0.82 (2H, m, C_7-H_b and C_6-H_b); 0.79 (3H, s, C_{13}-H_3). ^{13}C NMR (62.5 MHz, $CDCl_3$): 167.2 (C_2); 150.1 (C=O); 135.2, 133.7, 129.7, 129.1, 128.4, 126.9, 126.2, 122 (CAr); 100.4 (C_{3a}); 88.2 (C_{4a}); 77.7 (C_{8a}); 48.1 (C_5); 46.1 (CH_2); 31.3 (C_6); 25.1 (C_7); 22.1 (C_{11}); 19.3 (C_{12}); 10.8 (C_{13}).
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